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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/788,779	SEIDMAN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 2/27/04 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/22/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

2. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR 1.821(d). See page 21 of the specification.

Claim Objections

3. Claim 14 is objected to because of the following informalities:

In claim 14, the recitation of "from a from said sample a cell sample" should read, e.g., "from a cell sample."

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No.

5,429,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '923 are inclusive of methods for diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy associated mutation in the RNA of an individual. It is noted that the claims of '923 do not recite packaging the reagent required to perform the diagnostic method in a kit. However, reagent kits for performing DNA diagnostic assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primers and probes required for the detection of hypertrophic cardiomyopathy associated-mutations in a kit for the expected benefits of convenience and cost-effectiveness. Further, the claims of '923 recite the use of primers for detecting the *B*-MHC mutations, but do not recite the specific primers of claim 18. However, the sequence of the *B*-MHC gene was known at the time the invention was made. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers for the amplification of *B*-MHC sequences. Accordingly, the claimed primers for amplifying regions of the *B*-MHC gene containing the recited mutations would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite over the recitation of "for facilitating the diagnosis of hypertrophic cardiomyopathy" and "thereby facilitating the diagnosis of hypertrophic cardiomyopathy" because, within the context of the claim, it is not clear as to what is intended to be meant by facilitating diagnosis. The claims do not clarify how the step of detecting a mutation facilitates diagnosis. Thereby, it is not clear as to whether the claims are intended to be limited to methods for diagnosing hypertrophic cardiomyopathy or to general methods for detecting a mutation in the βMHC gene.

Claims 14 and 15 are indefinite over the recitation of "the β cardiac myosin heavy-chain RNA" because this phrase lacks proper antecedent basis. Additionally, it is unclear as to how the recitation of "A method of claim 1...and diagnosing the subject" is intended to further limit the claim. It is unclear as to whether the claim is intended to be drawn to a method of diagnosis such that the claim includes an additional active process step of diagnosing a subject.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods, primers and kits for detecting the presence of a beta cardiac myosin heavy-chain mutation (βMHC) mutation associated with hypertrophic cardiomyopathy (HCM) wherein the mutation is G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A, does not reasonably provide enablement for methods, primers or kits for detecting the presence or absence of any mutation in the βMHC gene associated with hypertrophic cardiomyopathy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to encompass methods, kits and primers for detecting the presence or absence of any mutation in the βMHC gene associated with hypertrophic cardiomyopathy. The claims do not define the mutation in terms of its nucleotide position or identity. Further, the claims encompass any type of mutation in the βMHC gene including missense mutations, insertions, deletions, and translocations.

Nature of the Invention

The claims are drawn to methods for detecting the presence or absence of a βMHC mutation associated with hypertrophic cardiomyopathy. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the analysis of the βMHC gene for the presence of mutations associated with HCM. The HCM affected members of 25 families were analyzed for the presence of mutations in the βMHC gene. Nine variants were identified, with 2 of the variants also being found in unaffected family members (pages 35-36). Each of the remaining 7 variants were point mutations which altered the coding sequence of the protein product. In particular, the specification teaches an association between the following mutations and the occurrence of HCM: G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A.

The post-filing date art indicates that the disclosure of 7 βMHC mutations is not representative of the broadly claimed genus of methods, primers and kits for detecting any βMHC gene mutation associated with HCM. In particular, Van Driest (JACC. 2004. 44: 602-610) teaches that there are 120 mutations in the βMHC gene that are correlated with HCM (see Figure 1 and page 609). Song (Clinica Chimica Acta. 2005. 351: 209-216) discloses 8 additional mutations in the βMHC gene (referred to therein as MYH7; see Table 1) that are correlated with HCM.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying novel mutations in a gene which are correlated with disease phenotypes is highly unpredictable. Knowledge of the sequence of the wildtype βMHC gene and other genes does not allow one to immediately envision specific mutations that are associated with the occurrence of HCM. Once a new mutation is identified, it remains unpredictable as to whether that mutation is sufficiently linked with a disease to be diagnostic for the disease.

The specification itself exemplifies the unpredictability in the art of identifying polymorphisms which are associated with a disease or phenotype. While the specification teaches 9 variants that were identified in the βMHC gene, 2 of these variants were found to be present in the unaffected population and are not considered to be correlated with the occurrence of HCM. The human genome contains polymorphisms at a frequency of approximately one polymorphism per 1000 nucleotides. Given the significantly large size of the βMHC gene (i.e., 22.9kb, spanning 38 exons), a significant number of variants in this gene are expected to be polymorphisms that are not correlated with HCM. The teachings of Van Driest (page 607) corroborate this finding in that Van Driest identified 21 polymorphisms in the βMHC gene that were present in both HCM patients and in control, unaffected individuals. Thereby, there is no predictable means to ascertain a priori whether a variant of the βMHC gene will or will not be associated with HCM.

The specification does not provide any specific information as to how the presence of the 7 mutations alter the functional activity of the protein encoded by the

βMHC gene or as to the role of these mutations in the development of HCM. The specification states that the 7 identified missense mutations were found in the head or head-rod junction of the βMHC gene. However, no information is provided regarding the how these regions are essential for functional activity and effect the development of HCM. Without extensive information regarding the structure-function relationship between the βMHC gene and HCM, it is highly unpredictable as to what would be the identity of additional mutant, allelic, or splice variants which would be associated with HCM. Thus, one cannot readily anticipate the effect of a polymorphism or mutation within the βMHC gene.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches only 7 mutations in the βMHC gene which are associated with HCM. To identify additional variants of the βMHC gene which are diagnostic would require extensive experimentation. For example, such experimentation may involve sequencing the βMHC gene of affected individuals having HCM, sequencing the βMHC gene of control individuals which do not have HCM, comparing the sequences of these two groups, and then identifying variations which are present only in the affected group and not in the control group. Such random, trial by error experimentation is considered to be undue.

While methods for identifying mutations are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may linked to a disease. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment.

The specification does not provide a predictable means for identifying additional variants of the βMHC gene and using these variants to screen for susceptibility to HCM.

Working Examples:

Again, the specification teaches methods for analyzing the nucleic acids of an individual to directly detect the presence of a G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A mutation in the βMHC gene as diagnostic of HCM. There are no additional examples provided in the specification in which HCM is diagnosed by detecting other mutations. Further, the specification does not exemplify any methods in which mutations other than base substitutions are detected as diagnostic of HCM. No insertions, deletions or translocations have been disclosed for the βMHC gene which would allow for the diagnosis of HCM.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only 7 missense mutations in the βMHC gene which are associated with HCM. The specification does not teach a representative number of mutations, including insertions, deletions, substitutions, splice variants, and gross chromosomal rearrangements which are associated with HCM.

Further, the specification does not teach each of the novel aspects of the claimed invention because the novelty of the invention lies in the identity of the specific mutations correlated with the occurrence of HCM. The novel aspects of the invention are not methods of identifying additional mutations in the βMHC gene since general methods of searching for mutations were known in the art at the time the invention was made.

In view of the unpredictability in the art, extensive experimentation would be required to identify additional variants of the βMHC gene which would be associated with and would be diagnostic for HCM. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

7. Claims 1-10, 12-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn broadly to encompass methods, kits and primers for detecting the presence or absence of any mutation in the βMHC gene associated with hypertrophic cardiomyopathy. The claims do not define the mutation in terms of its nucleotide position or identity. Further, the claims encompass any type of mutation in the βMHC gene including missense mutations, insertions, deletions, and translocations.

The specification teaches an association between the occurrence of HCM and the βMHC missense mutations G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A. Accordingly, methods, primers and kits for detecting the βMHC mutations G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A meet the written description requirements of 35 U.S.C. 112, first paragraph. However, the specification does not disclose and fully characterize the genus required by the claims of any mutation in the βMHC gene associated with HCM.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written

description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 7 members of the genus of βMHC missense mutations have been identified. No additional missense mutations or other types of mutations have been disclosed. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any additional βMHC gene mutations. However, the claims as written are inclusive of a very large genus of mutations in the βMHC gene. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in the βMHC gene, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with HCM. Rather, mutations in the βMHC gene associated with HCM represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations.

Accordingly, knowledge of the sequence of the wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

Further, the specification teaches mutations present in the head and head-rod region of the βMHC gene. No mutations have been identified in other portions of the βMHC gene, in intron sequences or 5' or 3' untranslated sequences. Additionally, the specification discloses only missense mutations in the βMHC gene. No other types of mutations, such as insertions, deletions, splice variants or translocations have been identified which are correlated with HCM.

The teachings in the post filing date art support the finding that the genus of mutations in the βMHC gene associated with HCM is large. In particular, Van Driest (JACC. 2004. 44: 602-610) teaches that there are 120 mutations in the βMHC gene that are correlated with HCM (see Figure 1 and page 609). Song (Clinica Chimica Acta. 2005. 351: 209-216) discloses 8 additional mutations in the βMHC gene (referred to therein as MYH7; see Table 1) that are correlated with HCM.

Accordingly, the disclosure in the specification of 7 missense mutations in the βMHC gene is not considered to constitute a representative number of nucleotide mutations, including insertions, deletions, substitutions or splice variants, in any exon,

intron or non-coding region of the βMHC gene or gross chromosomal rearrangements in the βMHC gene which are associated with HCM. For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 and 17 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman (Basic Research Cardiology. March/April 1992. 87: 106-112).

Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 109). Because the primers of Friedman amplify nucleic acids of *B*-MHC, the primers have the inherent property of being capable of detecting mutations in the *B*-MHC gene, including hypertrophic cardiomyopathy-

associated mutations. Accordingly, Friedman anticipates the invention of claims 16 and 17.

9. Claims 16 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman (Circulation. 1991. 83: 1866-1872).

Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 1867). Because the primers of Feldman amplify nucleic acids of *B*-MHC, the primers have the inherent property of being capable of detecting mutations in the *B*-MHC gene, including hypertrophic cardiomyopathy-associated mutations. The compositions of Feldman contain 13 pmol of each primer and therefore are considered to comprise at least 4 oligonucleotides. Accordingly, Feldman anticipates the invention of claims 16 and 17.

10. Claims 1-18 are rejected under 35 U.S.C. § 102(a) as being anticipated by Rosenzweig et al (New England Journal of Medicine ((1991) 325: 1753-1760; cited in the IDS).

Rosenzweig (p. 1754) teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using an RNA probe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy. In particular, Rosenzweig (see, e.g., Figure 1 and page 1757-1758) teaches the detection of a G832A and G1294A mutation as indicative of HCM. With respect to claims 16-18, the reference further teaches 4 oligonucleotide primers for amplifying the *B*-MHC gene and RNA probes which are complementary to at least a portion of the *B*-

MHC gene and which consist of the sequences of present SEQ ID NO: 1-10 (see page 1754, col. 2).

It is noted that the authorship of the Rosenzweig reference is distinct from the inventorship of the present application. Further, it is pointed out that while a 132 declaration was filed in the parent application to remove the Rosenzweig reference as prior art, affidavits or declarations, such as those submitted under 37 CFR 1.130, 1.131, and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application.

11. Claims 1-18 are rejected under 35 U.S.C. § 102(a) as being anticipated by Watkins et al. (New England Journal of Medicine (1992) 326:1108-1114; cited in the IDS).

Watkins (p. 1109) teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using a riboprobe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy. In particular, Watkins teaches methods for diagnosing HCM wherein the methods comprise detecting the βMHC mutations G832A, G1294A, C1443T, G1836C, G1902A, G2856A or G2931A (Table 1). The reference further teaches sets of nested oligonucleotide PCR primers for amplifying the *B*-MHC gene and RNA probes which are complementary to at least a portion of the *B*-MHC gene and which consist of the same nucleotide sequences as those of present SEQ ID NO: 1-10 (see Figure 1A, page 1109, col. 2).

12. Claims 1-4, 9, 12-16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Perryman (Circulation. October 1991. Vol. 84, page II-418, Abstract 1666).

Perryman teaches methods for detecting the presence of a mutation associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutation in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy, amplifying the DNA by PCR, and digesting the DNA with the restriction endonucleases DdeI or RsaI in order to detect the presence of said mutation. In particular, Perryman teaches detecting the presence of the previously disclosed A to G missense mutation in exon 13 (nucleotide 1294), which leads to an Arg to Gln substitution at amino acid 403 of the encoded protein. The method of Perryman detects the mutation in multiple copies of the DNA and thereby detects the mutation in more than one target sequence. The reference teaches that, while the mutation is uncommon, it is present only in HCM affected individuals and is not present in normal, control individuals. Accordingly, it is a property of the mutation that it is associated with HCM. Thereby, Perryman teaches a method for detecting the presence or absence of a mutation associated with hypertrophic cardiomyopathy for facilitating the diagnosis of hypertrophic cardiomyopathy wherein the method comprises amplifying *B*-MHC DNA and detecting the presence of a mutation associated with HCM.

With respect to claims 12 and 13, the method of Perryman detects the mutation in multiple copies of the DNA and thereby detects the mutation in more than one target sequence. With respect to claims 14 and 15, the method of Perryman is one in which a sample is obtained from a subject being tested for HCM. With respect to claims 16 and 17, Perryman teaches the use of a set of oligonucleotide primers for amplifying *B*-MHC nucleic acids, wherein the set contains multiple copies of primers and thereby includes at least 4 oligonucleotides.

13. Claims 1-4, 9, 12-16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Marian (Circulation. October 1992. Vol. 86, page I-16, Abstract 0061).

Marian teaches methods for detecting the presence of a mutation associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutation in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy, amplifying the DNA by PCR, and digesting the DNA with a restriction endonuclease in order to detect the presence of said mutation. In particular, Marian teaches detecting the presence of the previously disclosed A to G missense mutation in exon 13 (nucleotide 1294), which leads to an Arg to Gln substitution at amino acid 403 of the encoded protein. The method of Marian detects the mutation in multiple copies of the DNA and thereby detects the mutation in more than one target sequence. The reference teaches that the mutation was detected in 30 affected individuals but was not present in normal, control individuals. Marian states that "This mutation is associated with a severe form of the disease with high penetrance and variable expressivity. Therefore, we recommend individuals from families with FHCM be screened for this mutation early in life and if positive should be prohibited from participation in strenuous combative sports, to attenuate the likelihood of sudden death." Accordingly, it is a property of the mutation disclosed by Marian that this mutation is associated with HCM, and particularly with FHCM. Thereby, Marian teaches a method for detecting the presence or absence of a mutation associated with hypertrophic cardiomyopathy for facilitating the diagnosis of hypertrophic cardiomyopathy wherein the method comprises amplifying *B*-MHC DNA and detecting the presence of a mutation associated with HCM.

With respect to claims 12 and 13, the method of Marian detects the mutation in multiple copies of the DNA and thereby detects the mutation in more than one target

sequence. With respect to claims 14 and 15, the method of Marian is one in which a sample is obtained from a subject being tested for HCM. With respect to claims 16 and 17, Marian teaches the use of a set of oligonucleotide primers for amplifying *B*-MHC nucleic acids, wherein the set contains multiple copies of primers and thereby includes at least 4 oligonucleotides.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Rosenzweig in view of the Stratagene Catalog.

Rosenzweig (p., 1754) teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using a riboprobe in a RNase protection assay in order to

detect the presence of point mutations associated with hypertrophic cardiomyopathy. The method of Rosenzweig requires the use of the reagents of primers for the amplification of *B*-MHC, riboprobes complementary to *B*-MHC DNA, and RNase to digest unhybridized RNA. Rosenzweig does not teach packaging the reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, riboprobe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to instructions, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)). However, in view of the conventionality in the analytical arts of including instructions in kits, it would have been further prima facia obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents.

15. Claims 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Watkins in view of the Stratagene Catalog.

Watkins teaches methods for diagnosing hypertrophic cardiomyopathy wherein the methods comprise the steps of isolating RNA from peripheral blood mononuclear

cells, reverse transcribing *B*-myosin heaving chain RNA to cDNA, amplifying the cDNA by nested PCR and detecting the amplified *B*-myosin heaving chain nucleic acids using a riboprobe in a RNase protection assay in order to detect the presence of point mutations associated with hypertrophic cardiomyopathy. The method of Watkins requires the use of the reagents of primers for the amplification of *B*-MHC, riboprobes complementary to *B*-MHC DNA, and RNase to digest unhybridized RNA. Watkins does not teach packaging the reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, riboprobe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to instructions, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)). However, in view of the conventionality in the analytical arts of including instructions in kits, it would have been further prima facia obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents.

16. Claims 1-6, 9, 10, 12-15, 16, and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance (cited in the IDS) in view of Mullis (U.S. Patent No. 4,683,195).

It is noted that the claims are drawn to methods for detecting the presence or absence of a mutation associated with HCM for facilitating diagnosis of HCM. The claims do not require the diagnosis of HCM and thereby are considered to include general methods which detect the presence of a mutation in the βMHC gene, wherein the mutation has the property of being associated with HCM.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer-Lowrance discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. The reference (see abstract) states that the "(I)dentification of two unique mutations within cardiac MHC genes in all individuals with FHC from two unrelated families demonstrates that defects in the cardiac MHC genes can cause this disease". Additionally, the reference (page 1003) states that "(t)he missense mutation occurs only in the β cardiac MHC gene of affected individuals." The reference also teaches that further assays should be performed to determine if the mutation is present in other families and states that use of genetic probes to MHC

mutations will be important in facilitating our understanding of the function of MHC and the causes of HC. Geisterfer-Lowrance does not teach amplifying the sample *B*-MHC nucleic acid prior to determining the sequence of the DNA.

Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis also teaches amplifying nucleic acids by PCR prior to sequencing (see column 36). The reference states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have amplified the βMHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of the point mutations in the βMHC nucleic acids. It is noted that it is a property of the Arg403Gln mutation that this mutation is associated with HCM.

With respect to claims 10 and 17, Mullis (col. 30) further teaches performing PCR using sets of nested primers in order to reduce the background in the amplification

process and thereby increase the overall specificity of the amplification reaction. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have used nested primers in the PCR amplification, and to thereby have designed a set of 4 oligonucleotide primers for amplifying the βMHC nucleic acids in order to have achieved the expected benefit expressly stated by Mullis of increasing the specificity of the amplification reaction and thereby of increasing the overall accuracy of the detection method.

17. Claims 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer-Lowrance discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. The reference (see abstract) states that the "(I)dentification of two unique mutations within cardiac MHC genes in all individuals with FHC from two unrelated families demonstrates that defects in the cardiac MHC genes can cause this disease". The reference teaches that further assays should be performed to determine if the mutation is present in other families and states that use of

genetic probes to MHC mutations will be important in facilitating our understanding of the function of MHC and the causes of HC. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic cardiomyopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B*-MHC nucleic acids.

18. Claims 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance (cited in the IDS) in view of Almoguera and further in view of the Stratagene Catalog (1988, page 39).

The teachings of Geisterfer-Lowrance and Almoguera are presented above. Modification of the method of Geisterfer-Lowrance as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected

benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify *B*-MHC nucleic acids and detect mutations in *B*-MHC nucleic acids. it is noted that it is a property of the Arg403Gln mutation that it is associated with hypertrophic cardiomyopathy. The teachings of Geisterfer-Lowrance of the presence of this mutation and its role in hypertrophic cardiomyopathy would have motivated the ordinary artisan to have generated kits that would have allowed for the amplification of *B*-MHC nucleic acids and the analysis of *B*-MHC nucleic acids for mutations.

With respect to instructions, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)). However, in view of the conventionality in the analytical arts of including instructions in kits, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit for the advantage of providing the practioner with information as to how to use the components of the kit.

19. Claims 5, 6, 10, 16 and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Perryman in view of Mullis (U.S. Patent No. 4,683,195).

The teachings of Perryman are presented above. Perryman does not specifically teach that the sample to be analyzed for a mutation is RNA obtained from a nucleated blood cell.

However, Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis

states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Perryman so as to have amplified the βMHC RNA by reverse transcription prior to PCR in order to have provided a source of larger quantities of nucleic acids that could be analyzed for the presence of the mutation, thereby increasing the overall sensitivity of the detection of the point mutations in the βMHC nucleic acids. It is noted that it is a property of the Arg403Gln mutation that this mutation is associated with HCM.

With respect to claim 6, Perryman does not specify the source of the sample and thereby does not teach analyzing nucleic acids obtained from nucleated blood cells. However, Mullis (paragraphs 11 and 137) teaches amplifying nucleic acids obtained from clinical blood samples, including sample nucleic acids isolated from blood lymphocyte (i.e., nucleated) cells. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Perryman to the analysis of RNA isolated from nucleated blood cells in order to have provided a non-invasive and readily available source of nucleic acids that could be used for the detection of the Arg403Gln βMHC mutation.

With respect to claims 10 and 17, Mullis (col. 30) further teaches performing PCR using sets of nested primers in order to reduce the background in the amplification process and thereby increase the overall specificity of the amplification reaction. Additionally, it is noted that the complete sequence of the βMHC gene was known at the time the invention was made. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Perryman so as to have used nested primers in the PCR amplification, and to thereby have designed a set of 4 oligonucleotide primers for amplifying the βMHC nucleic acids in order to have achieved the expected benefit expressly stated by Mullis of increasing the specificity of the amplification reaction and thereby of increasing the overall accuracy of the detection method.

20. Claims 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Perryman in view of Almoguera.

The teachings of Perryman are presented above. In particular, Perryman teaches detecting the Arg403Gln βMHC mutation by PCR, followed by restriction enzyme digestion. Perryman does not teach detecting point mutations associated with hypertrophic cardiomyopathy by performing a RNase protection assay on amplified βMHC nucleic acids.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage

of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Perryman so as to have detected the mutations associated with hypertrophic cardiomyopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B*-MHC nucleic acids.

21. Claims 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Perryman in view of Almoguera and further in view of the Stratagene Catalog (1988, page 39).

The teachings of Perryman and Almoguera are presented above. Modification of the method of Perryman as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the

B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify *B*-MHC nucleic acids and detect mutations in *B*-MHC nucleic acids. it is noted that it is a property of the Arg403Gln mutation that it is associated with hypertrophic cardiomyopathy. The teachings of Perryman of the presence of this mutation and its role in hypertrophic cardiomyopathy would have motivated the ordinary artisan to have generated kits that would have allowed for the amplification of *B*-MHC nucleic acids and the analysis of *B*-MHC nucleic acids for mutations.

With respect to instructions, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight

(see MPEP 706.03(a)). However, in view of the conventionality in the analytical arts of including instructions in kits, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit for the advantage of providing the practioner with information as to how to use the components of the kit.

22. Claims 5, 6, 10, 16 and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Marian in view of Mullis (U.S. Patent No. 4,683,195).

The teachings of Marian are presented above. Marian does not specifically teach that the sample to be analyzed for a mutation is RNA obtained from a nucleated blood cell.

However, Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Marian so as to have amplified the βMHC RNA by reverse transcription prior to PCR in order to have provided

a source of larger quantities of nucleic acids that could be analyzed for the presence of the mutation, thereby increasing the overall sensitivity of the detection of the point mutations in the βMHC nucleic acids. It is noted that it is a property of the Arg403Gln mutation that this mutation is associated with HCM.

With respect to claim 6, Marian does not specify the source of the sample and thereby does not teach analyzing nucleic acids obtained from nucleated blood cells. However, Mullis (paragraphs 11 and 137) teaches amplifying nucleic acids obtained from clinical blood samples, including sample nucleic acids isolated from blood lymphocyte (i.e., nucleated) cells. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Marian to the analysis of RNA isolated from nucleated blood cells in order to have provided a non-invasive and readily available source of nucleic acids that could be used for the detection of the Arg403Gln βMHC mutation.

With respect to claims 10 and 17, Mullis (col. 30) further teaches performing PCR using sets of nested primers in order to reduce the background in the amplification process and thereby increase the overall specificity of the amplification reaction. Additionally, it is noted that the complete sequence of the βMHC gene was known at the time the invention was made. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Marian so as to have used nested primers in the PCR amplification, and to thereby have designed a set of 4 oligonucleotide primers for amplifying the βMHC nucleic acids in order to have achieved the expected benefit expressly stated by Mullis

of increasing the specificity of the amplification reaction and thereby of increasing the overall accuracy of the detection method.

23. Claims 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Marian in view of Almoguera.

The teachings of Marian are presented above. In particular, Marian teaches detecting the Arg403Gln βMHC mutation by PCR, followed by restriction enzyme digestion. Marian does not teach detecting point mutations associated with hypertrophic cardiomyopathy by performing a RNase protection assay on amplified βMHC nucleic acids.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Marian so as to have detected the mutations associated with hypertrophic cardiomyopathy in *B*-MHC nucleic acids by amplifying the nucleic acids by PCR and

detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B*-MHC nucleic acids.

24. Claims 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Marian in view of Almoguera and further in view of the Stratagene Catalog (1988, page 39).

The teachings of Marian and Almoguera are presented above. Modification of the method of Marian as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the B-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-

assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify *B*-MHC nucleic acids and detect mutations in *B*-MHC nucleic acids. it is noted that it is a property of the Arg403Gln mutation that it is associated with hypertrophic cardiomyopathy. The teachings of Marian of the presence of this mutation and its role in hypertrophic cardiomyopathy would have motivated the ordinary artisan to have generated kits that would have allowed for the amplification of *B*-MHC nucleic acids and the analysis of *B*-MHC nucleic acids for mutations.

With respect to instructions, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)). However, in view of the conventionality in the analytical arts of including instructions in kits, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit for the advantage of providing the practioner with information as to how to use the components of the kit.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
November 14, 2005

CARLA J. MYERS
PRIMARY EXAMINER

George C. Elliott, Ph.D
Director
Technology Center 1600